R E M A R K S

Applicants would like to thank Examiners Lucas and Housel for their time and helpful suggestions with the interview of September 11, 2003. The issues addressed during the interview and the rejections of the Office Action are discussed below.

Claims 1, 4-7 and 10-13 are pending in the application, with claim 1 being amended and claims 10-13 being newly added. New claims 10-13 are drawn more specifically to methods of treating diseases associated with demylination in the central nervous system or MS by administering anti-Fas ligand antibodies. New claims 10-13 in no way add new matter. As such, entry and consideration thereof are respectfully requested.

Rejection under 35 U.S.C.§112, 1st paragraph

The Examiner newly rejects claims 1 and 5-7 under 35 U.S.C.§112, 1st paragraph for lack of enablement with the assertion that the specification is only enabled for treating an autoimmune demyelinating disease using anti-Fas ligand antibodies.

This rejection was discussed during the September 11, 2003 interview, at which time the following concerns of the Examiner were raised and addressed.

a) *Identity of the Fas antagonist* - During the interview, the Examiner suggested that it would be unpredictable as to what effect other Fas antagonists would have on treating autoimmune demylinating diseases. However, as Applicants discussed during the interview, if the antibodies in the Examples block the physical binding of Fas and Fas ligand so that the Fas ligand can no longer bind to the Fas, one skilled in the art would expect that other substances, which also block the physical binding would have the same effect.

Applicants believe that the Examiner agreed with this position; but raised a concern that the claims could be interpreted as encompassing a situation where the inhibition of Fas-Fas ligand binding is not through competitive inhibition, i.e. not through the direct blocking of Fas to Fas-ligand. The Examiner also raised a concern that the claims encompass the situation where the Fas antagonist binds to Fas and partially blocks Fas ligand binding but also some how effects signaling through the Fas molecule, with the efficacy in treatment coming from the antagonist binding to Fas, not the blocking of the Fas-Fas ligand binding per se.

During the interview, the Examiner and his supervisor suggested these issues be addressed by more specifically defining

the mechanism by which the Fas antagonist acts. Claim 1 thusly has been amended to define the Fas antagonist as "a substance that binds to Fas ligand and inhibits Fas-Fas ligand binding."

b) Diseases to be treated - The second concern raised by the Examiner during the interview regarding 35 U.S.C. §112, 1st paragraph regards the enablement of treating various diseases. The Examiner suggested that because of the ambiguity in the field of MS and autoimmune demyelinating diseases, one skilled in the art would be surprised by the results of the Examples and would not necessarily expect the same efficacy with other diseases. The Examiner also raised a concern with the apparent teachings in Chu that apoptosis should be stimulated to treat MS. The Examiner notes in the Interview Summary Record that the results in Chu are not inconsistent with the claimed invention. To address this issue the Examiner suggested that the claims should be amended to more clearly state that the apoptosis of oligodentritic cells or myelin sheath cells is being suppressed with the invention. Claim 1 has been further amended as suggested by the Examiner to recite that apoptosis of myelin sheath cells is being suppressed.

Finally, the Examiner has raised a concern as to the breath of applicability of the experiments in the specification and whether the rat model of the specification is the model of only MS or is a model for other diseases as well. Attached hereto as Exhibit A, is the MeSH heading from NCBI database for EAE (the rat model of the examples.) As seen from the MeSH heading printout, the EAE model is used for diseases involving the demylination of the CNS. In addition, Elliot et al. on page 1602, right column, lines 1-4, confirm that EAE is considered a model of pathological demylination of the CNS generally.

Thus, for the reasons discussed above, the invention as claimed is fully enabled and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C.§103

Claims 1 and 5-7 remain rejected under 35 U.S.C. §103 as being obvious over D'Souza and Wallach et al. (U.S. Pat. No. '327) combined with Lynch. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As explained during the Interview, Applicants do not assert that the data in D'Souza is wrong per se, but rather that the conclusions reached by D'Souza based on their data is controversial and questioned by other scientists. Applicants previously submitted Elliot et al. as evidence of the controversy in the field. In addition, submitted with the present response as Exhibit B (Clark et al. Clin. Immunol. and Pathol. 85:315-319 (1997) and Malipiero et al. Eur. J. Immunol. 27:3151-3160 (1997)), are two addition journal articles, which clearly show that the conclusions by D'Souza were regarded at the time of the invention to be highly controversial.

Clark et al. and Malipiero et al. support the existence of controversy of the field and the unpredictability associated with the field of the invention. Applicants note that both references acknowledge the work by D'Souza et al. In addition, both references indicate that the postulation by D'Souza et al. regarding the Fas-FasL involvement in MS was based on the observations that

a) there is an increased expression of Fas and FasL on certain cell subpopulations in MS patients and

b) the ability of Fas ligation using anti-Fas antibodies to induce oligdendrocyte cell death *in vitro*.

However, that Clark et al. Clin. Immunol. reiterate on page 317, right column, that the *in vitro* cell death observed by D'Souza et al. was not through apoptosis. In addition, both Clark et al. and Malipiero et al. question the asserted role of Fas/FasL mediated apoptosis in MS and indicate that the results of D'Souza were inconclusive. Both references further conclude that Fas/FasL is not involved in EAE pathogenesis. Thus, these references support the position that the field was unpredictable at the time of the invention and the results of D'Souza were, at best, inconclusive. As such, one skilled in the art would have no expectation of success in treating autoimmune demyelinating diseases with a substance that inhibits Fas-Fas ligand binding.

When D'Souza et al. is taken in full consideration with the teachings of Elliot et al. and the new references of Clark et al. and Malipiero et al., one skilled in the art would reach the conclusion that there was a lot of ambiguity in the field regarding the role of the Fas-Fas ligand pathway in MS at the time of the invention. As such, one skilled in the art would not have any reasonable expectation of success prior to actually performing experiments, as was done by the inventors. As such, the present invention is not obvious over the cited references and withdrawal of the rejection is respectfully requested.

Should the Examiner have any questions regarding the present application, he is requested to please contact MaryAnne Armstrong, Ph.D. (Reg. No. 40,069), in the Washington DC area, at (703) 205-8000.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of $110.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Gerald M. Murphy, Jr., #28,977

MaryAnne Armstrong, PhD #40,069

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/MAA:bmp
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Attachments: Exhibits A and B